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ORIGINAL ARTICLE

Management of brain metastases from large cell neuroendocrine carcinoma of the lung: improved outcomes with radiosurgery

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ABSTRACT

Objectives: Large cell neuroendocrine carcinoma (LCNEC) of the lung is a rare pulmonary tumor, having similar natural history and management strategy as small cell lung cancer. Therefore, the management of brain metastases in these patients has mirrored that of SCLC through the use of whole brain radiation therapy (WBRT). We used the National Cancer Database (NCDB) to look at predictors of stereotactic radiosurgery (SRS) and any potential differences in outcomes for patients with brain metastases from LCNEC.

Material and methods: We queried the NCDB from 2004 to 2015 for patients with LCNEC of the lung with brain metastases that received brain radiation. Univariable and multivariable analyses were performed to identify factors predictive of SRS use and overall survival (OS). Propensity-adjusted Cox proportional hazard ratios for survival were used to account for indication bias.

Results: Out of 9970 patients with LCNEC of the lung we identified 348 with brain metastases. Sixty-eight patients were treated with upfront SRS and 280 were treated with WBRT. Patients that were treated at an academic facility or received chemotherapy as part of upfront treatment were more likely to receive SRS. Univariable analysis revealed improved outcomes with SRS compared to WBRT, with a median OS of 11 months compared to 6 months, respectively ($p = .007$). Multivariable Cox regression with propensity score confirmed SRS to have improved survival (HR: 0.68, 95%CI: 0.51–0.91, $p = .0093$). Multivariable Cox regression with propensity score also identified younger age, receipt of chemotherapy, absence of extracranial disease and non-rural locations as additional predictors of improved OS.

Conclusions: Treatment of brain metastases from LCNEC of the lung with SRS was associated with improved survival. For the appropriate patients, upfront treatment of limited brain metastases with SRS may be appropriate.

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Introduction

Large cell neuroendocrine carcinoma (LCNEC) of the lung is a rare pulmonary tumor characterized by the presence of both neuroendocrine morphology and immunohistochemical evidence of neurochemical markers, not meeting criteria for the better recognized small cell lung cancer (SCLC) [1]. Regardless, the natural history of LCNEC of the lung is similar to SCLC, with a key difference being that it is more likely to present at stages 1–3 [2]. Brain metastases are very common in SCLC, to the point that an overall survival (OS) benefit has been shown for the use of prophylactic cranial irradiation, which in turn provides a rationale for whole brain radiation therapy (WBRT) in the presence of even isolated brain metastases [3,4]. This thought process has been extrapolated to LCNEC, with most institutions favoring a whole brain approach [5,6]. In the setting of limited brain metastases in SCLC, emerging data provides supporting evidence for use of stereotactic radiosurgery (SRS) with subsequent close surveillance, in lieu of WBRT, to reduce the risk of long-term neurocognitive sequelae associated with its use [7,8]. To that end, there are some series showing similar rates of control with the use of SRS in patients with brain metastases from LCNEC of the lung [9]. In the present study, we utilized the National Cancer Database (NCDB) to examine trends and outcomes in the management of brain metastases from LCNEC of the lung.

Material and methods

We conducted a retrospective review using de-identified data from the NCDB, which is exempt from IRB oversight. The NCDB is a tumor registry jointly maintained by the American Cancer Society and the American College of Surgeons for more than 1500 hospitals accredited by the Commission on Cancer. The database captures up to an estimated 70% of newly diagnosed malignancies each year in

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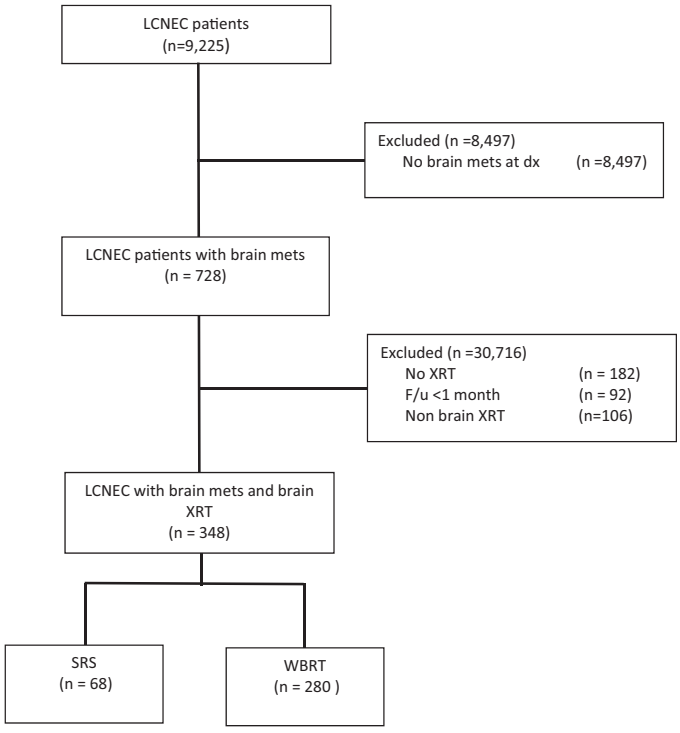

Figure 1. CONSORT diagram.

the USA. We queried the database for patients with documented brain metastases at diagnosis from LCNEC of the lung (ICD-0-3 histology code 8013). Figure 1 is a consort diagram outlining the cohort selection criteria. The database contained patient data form 2004 to 2015, however, brain metastases were not documented until 2010. We excluded any patients that did not have brain metastases at diagnosis, no history of brain radiation, and follow-up <1 month to account for immortal time bias.

Race was categorized as White, African American, or Other. Comorbidity was quantified using the Charlson/Deyo comorbidity index [10]. Socioeconomic data in the patients' residence census tract were provided as quartiles of the percentage of persons with less than a high school education and median household income. The facility type was assigned according to the Commission on Cancer accreditation category. Locations were assigned based on data provided by the US Department of Agriculture Economic Research Service. Insurance status is documented in the NCDB as it appears on the admission page. The data used in the study are derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator.

Data were analyzed using Medcalc Version 18 (Ostend, Belgium). Summary statistics are presented for discrete variables. χ^2 tests compared sociodemographic, treatment, and tumor characteristics between the treatment groups. OS was calculated in months from time of diagnosis to date of last contact or death. Kaplan–Meier curves were used to calculate cumulative probability of survival [11]. Log-rank statistics were used to test whether there was a statistically significant difference in the cumulative proportions across groups. A Cox proportional hazards model was used for multivariable survival analysis [12]. Due to the large nature of the dataset, factors significant on univariable analysis were entered using a stepwise backward elimination process. Adjusted hazard ratios and 95% confidence intervals are reported, using an α level of 0.05 to indicate statistical significance.

Propensity score-matched survival analysis was used to account for indication bias due to lack of randomization between patients receiving WBRT or SRS [13]. Multivariable logistic regression was used to calculate a propensity score indicative of conditional probability of receiving WBRT or SRS. The propensity model included observable variables associated with treatment selection on multivariable logistic regression. A Cox proportional hazards model was then constructed incorporating the propensity score, but also

Table 1. Patient demographics and clinical characteristics at baseline ($n = 348$).

Characteristics	No. (%)
Sex	
Male	170 (49)
Female	178 (51)
Race	
White	295 (85)
African American	47 (14)
Other	6 (1)
Comorbidity score	
0	211 (61)
1	99 (28)
≥2	38 (11)
Insurance	
Not insured	13 (4)
Private payer	103 (30)
Government	226 (65)
Unrecorded	6 (1)
Education, %	
≥29	61 (18)
20–28.9	104 (30)
14–19.9	113 (32)
<14	70 (20)
Treatment facility type	
Community cancer program	26 (7)
Comprehensive community cancer program	132 (38)
Academic/research program	190 (55)
Treatment facility location	
Metro	282 (81)
Urban	51 (15)
Rural	2 (0.5)
Unrecorded	13 (3.5)
Income, USD	
<30,000	65 (19)
30,000–35,000	96 (28)
35,000–45,999	86 (25)
>46,000	100 (27.5)
Unrecorded	1 (0.5)
Distance to treatment facility, miles	
≤10	167 (48)
>10	181 (52)
Age distribution, years	
≤65	187 (54)
>65	161 (46)
Year of diagnosis	
2010	55 (16)
2011	55 (16)
2012	58 (17)
2013	97 (28)
2014	83 (23)
Extracranial metastatic disease	
No	237 (68)
Yes	111 (32)

Table 2. Comparative use of SRS by baseline characteristics in patients receiving brain radiation.

Characteristic	SRS ($n = 68$) (%)	WBRT ($n = 280$) (%)	Odds ratio	95% CI	p
Sex					
Male	32 (47)	138 (49)	1	Reference	
Female	36 (53)	142 (51)	1.09	0.64–1.86	.74
Race					
White	52 (76)	243 (87)	1	Reference	
African American	13 (19)	34 (12)	1.78	0.88–3.62	.11
Other	3 (5)	3 (1)	4.67	0.91–23.8	.063
Comorbidity score					
0	42 (62)	169 (60)	1	Reference	
1	17 (25)	82 (29)	0.83	0.45–1.55	.57
≥2	9 (13)	29 (11)	1.25	0.55–2.83	.60
Age					
≤65	38 (56)	149 (53)	1	Reference	
>65	30 (44)	131 (47)	0.89	0.52–1.53	.69
Insurance					
None	2 (3)	11 (4)	1	Reference	
Private payer	23 (34)	80 (29)	1.58	0.33–7.65	.57
Government	40 (59)	186 (66)	1.18	0.25–5.54	.83
Unknown	3 (4)	3 (1)	5.50	0.61–49.5	.13
Education					
≥29%	7 (10)	54 (19)	1	Reference	
20–28.9	20 (29)	84 (23)	1.84	0.73–4.64	.19
14–19.9	22 (32)	91 (33)	1.87	0.75–4.66	.18
<14	19 (29)	51 (25)	2.87	1.11–7.41	.029
Facility type					
Community Cancer Program	0 (10)	26 (10)	1	Reference	
Comprehensive Cancer Program	17 (54)	115 (47)	8.03	0.47–137.8	.15
Academic/Research Program	51 (36)	139 (43)	19.56	1.17–326.9	.0385
Facility location					
Metro	59 (92)	223 (82)	1	Reference	
Urban	5 (8)	46 (17)	0.41	0.15–1.08	.071
Rural	0 (0)	2 (1)	0.75	0.04–15.86	.85
Income, USD					
<30,000	10 (15)	55 (20)	1	Reference	
30,000–35,000	12 (18)	84 (30)	0.79	0.32–1.94	.60
35,000–45,999	20 (30)	66 (24)	1.67	0.72–3.86	.23
>46,000	26 (37)	74 (26)	1.93	0.86–4.34	.11
Extracranial metastases					
No	50 (74)	187 (67)	1	Reference	
Yes	18 (26)	93 (33)	0.72	0.39–1.31	.29
Distant to facility					
≤10 miles	29 (52)	138 (60)	1	Reference	
>10 miles	39 (48)	142 (40)	1.31	0.77–2.23	.33
Received chemotherapy					
No	16 (24)	106 (38)	1	Reference	
Yes	52 (76)	174 (62)	1.98	1.08–3.64	.028
Year of diagnosis					
2010	10 (15)	45 (16)	1	Reference	
2011	10 (15)	45 (16)	1.00	0.38–2.63	1.0
2012	7 (10)	51 (18)	0.62	0.22–1.76	.37
2013	21 (31)	76 (27)	1.24	0.54–2.88	.61
2014	20 (29)	63 (23)	1.43	0.61–3.34	.41

Education is quartiles of the percentage of persons with less than a high school education in the patients' residence census tract. Income is median household income in the patients' residence census tract.

excluding factors included in the propensity score calculation to avoid overcorrection. The assumption of balance was further validated by stratifying the data into propensity score-based quintiles, and confirming that the difference in propensity score mean per quintile was <0.10.

Results

Baseline patient characteristics are outlined in Table 1. Between 2010 and 2015, 348 patients had brain metastases at diagnosis out of 5143 (15%). The median WBRT dose was 30 Gy (interquartile range: 30–35 Gy). The median SRS dose was 22 Gy (interquartile range: 18–30 Gy). Radiation was initiated at a median 21 days after diagnosis (interquartile range: 7–43 days). Two hundred twenty-six patients (65%) received chemotherapy as part of their initial treatment strategy, with systemic therapy starting a median 47 days after diagnosis (interquartile range: 31–63 days). The odds of receiving SRS increased with treatment at an academic facility, increased patient education level, and receipt of chemotherapy (Table 2). The rate of SRS use increased slightly over time, with 18% of brain metastases patients receiving SRS in 2010 and 24% receiving SRS in 2015.

The median follow-up time was 7 months (1–77 months). One and three-year OS for all patients were 33% and 7%, respectively. Patients treated with SRS had improved OS compared to WBRT [median 11 months versus 6 months, $p = .007$ (Figure 2)]. Multivariable Cox regression revealed

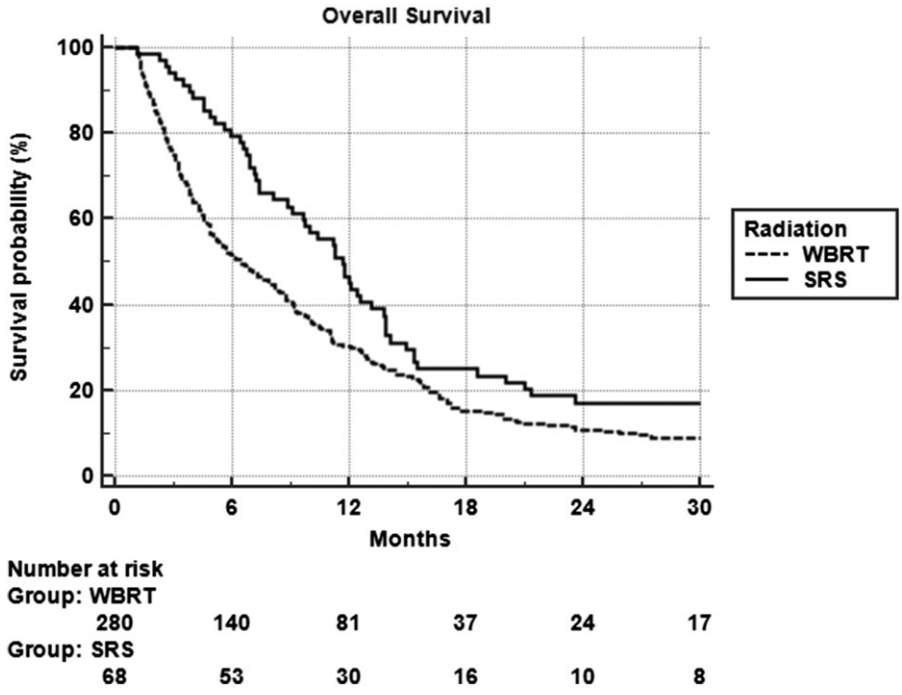

Figure 2. OS by type of brain radiation. Median survival was 11 months compared to 6 months in favor of SRS, $p = .007$.

increased age, no chemotherapy, extracranial disease, WBRT, decreased income, and rural location to be associated with decreased survival (Table 3). A second multivariable Cox proportional hazards model was used including the propensity score. The propensity score adjusted multivariable analysis identified SRS, younger age, receipt of chemotherap, non-rural location, and no extracranial disease as predictors for improved survival (Table 3).

Discussion

LCNEC of lung is a rare pulmonary tumor, as evidenced by <10,000 documented cases in the NCDB between 2004 and 2015. It is diagnosed based on high-grade features and presence of neuroendocrine markers and morphology, although not meeting criteria to be classified as SCLC [2]. The prognosis of LCNEC of the lung is poor, and a SEER analysis using multivariate analysis did not show any difference in survival comparing LCNEC to SCLC [14]. As such, the management of advanced LCNEC of the lung typically mimics that of SCLC [15]. Brain metastases are not uncommon at time of diagnosis for SCLC, with studies quoting rates in the range of 10% [16]. Reviewing the NCDB SCLC series from 2004 to 2014 (keeping in mind brain metastases not tracked until 2010), the rate of documented brain metastases at diagnosis was 15%, identical to the rate seen in the present NCDB analysis for LCNEC.

It is well known that even in patients without brain metastases at diagnosis of SCLC, the metastatic propensity of the disease is sufficiently high to warrant prophylactic treatment of the whole brain. The benefit is well documented in the classic meta-analysis examining outcomes in close to 1000 patients over seven trials treated prophylactically in limited stage SCLC, with an absolute survival benefit of 5% at 3 years [3]. Even in extensive stage SCLC, there is some evidence for potential benefit. The study by Slotman et al. showed a doubling in survival at 1 year and reduction in symptomatic brain metastases from 40% to 15% through the use of PCI in patients with extensive stage SCLC having a response to chemotherapy [17]. Though generally received favorably, the major criticism of that study was the failure to reimage the brain prior to PCI, as such, a more recent Japanese study in an identical patient population did include that testing in the schema [18]. OS was not improved with PCI in that series, but it should be noted that without PCI the incidence of brain metastases was 59% compared to 33%.

Notwithstanding, WBRT does not come without its share of potentially undesirable side effects, some of which can be permanent such as neurocognitive decline. This notion is well demonstrated in the MD Anderson series comparing WBRT + SRS to SRS alone for patients with 1–3 brain metastases [19]. In that study, patients treated with WBRT in addition to SRS showed a greater risk of significant decline in learning and memory function at 4 months compared to those patients not receiving WBRT. In more recent years, consideration of SRS alone for brain metastases from SCLC has been explored both in the literature and in practice at different institutions. One of the original series by Wegner et al. showed improved survival with a combined WBRT and Gamma Knife SRS approach, with a median survival of 14 months compared to 6 months [8]. In addition, local control was excellent at 86% at 1 year. A similar series by Olson et al. also examined linear accelerator based SRS in the treatment of brain metastases from SCLC, again showing high rates of local control at 76% (granted all patients in this particular series had past WBRT) [20]. As expected, in both of these series, the rate of distant brain failure was 60% at 4–6 months post-SRS (in line with the PCI data mentioned

Table 3. Multivariable cox proportional hazards models for overall survival in patients receiving SRS for brain metastases from large cell neuroendocrine carcinoma.

Significant characteristics	Hazard of death (95% CI)	*p*
Cox model without propensity score		
Age		
≤65	Reference	
>65	1.50 (1.15–1.97)	.0031
Chemotherapy		
No	Reference	
Yes	0.40 (0.31–0.52)	<.0001
Extracranial disease		
Yes	Reference	
No	2.31 (1.79–2.98)	<.0001
Radiation type		
WBRT	Reference	
SRS	0.68 (0.51–0.91)	.01
Income, USD		
<30,000	Reference	
30,000–35,000	1.31 (0.86–1.99)	.20
35,000–45,999	1.52 (1.15–2.02)	.0039
>46,000	1.29 (0.98–1.71)	.066
Location		
Metro	Reference	
Urban	1.28 (0.87–1.87)	.21
Rural	8.91 (2.13–37.25)	.0027
Years of diagnosis		
2010	Reference	
2011	1.54 (1.11–2.15)	.0104
2012	1.40 (1.00–1.96)	.0499
2013	1.30 (0.97–1.73)	.08
2014	1.14 (0.75–1.71)	.55
Cox model with propensity score		
Age		
≤65	Reference	
>65	1.53 (1.17–1.99)	.0017
Radiation		
WBRT	Reference	
SRS	0.68 (0.51–0.91)	.0093
Chemo		
No	Reference	
Yes	0.44 (0.34–0.56)	<.0001
Location		
Metro	Reference	
Urban	1.26 (0.88–1.82)	.21
Rural	7.48 (1.81–30.8)	.0054
Extracranial disease		
No	Reference	
Yes	2.03 (1.59–2.59)	<.0001

above), highlighting the need for careful and regular surveillance with brain imaging when utilizing a SRS approach. This approach has also been examined using the NCDB, with results having been published within the last year [7]. In that analysis, up front brain SRS was used in 200 of 5952 patients with brain metastases from SCLC. SRS was associated with improved OS (median 10.8 months vs. 7.1 months) on both univariate and multivariate testing with propensity score matching. Granted, these data must be interpreted with some caution as the NCDB lacks information on performance status, number of brain metastases, local and distant failure, and any salvage therapy.

As alluded to above, brain metastases from pulmonary LCNEC have typically been managed similarly to SCLC. A Canadian series examined outcomes in close to 100 patients with LCNEC of the lung, noting that nearly one-third of patients presented with stage IV disease [21]. Furthermore, approximately 40% of patients developed brain metastases in follow-up. Given that finding, the authors concluded that PCI should be investigated as a possible means of improving outcomes in this patient population. Additionally, an Italian study which retrospectively reviewed 72 patients with stage III–IV LCNEC of the lung treated similarly to SCLC, including the addition of PCI [22]. With the addition of PCI, patients with LCNEC of the lung experienced improved OS, 33.4 months vs. 8.6 months ($p = .05$), further supporting use of WBRT. That being said, SRS alone has also been evaluated in the treatment of brain metastases from LCNEC. The largest series comes from 21 Gamma Knife centers in Japan and examined outcomes in 101 patients treated with up front SRS. Of note, 25% of patients in this series had brain metastases at diagnosis [9]. The local control was an excellent 86% at 1 year. Development of new brain metastases was in the 40–50% range at 1–2 years. The group from Cleveland Clinic also published their series which included 29 patients with brain metastases from LCNEC managed in a heterogeneous fashion (55% WBRT, 28% SRS alone and 17% combination) [23]. Interestingly, the patients managed with SRS alone had similar rates of distant brain failure compared to those treated with WBRT (25% and 32%, respectively), keeping in mind the sample size was rather small. Based on their results, the authors concluded that the pattern of failure for LCNEC of the lung is perhaps more similar to that of NSCLC, and hence SRS alone would be a reasonable approach.

The results of this NCDB analysis certainly lend further support to the notion that SRS can be an effective and reasonable up front approach in patients with brain metastases from LCNEC. It is noteworthy that an OS advantage was found with the use of SRS, even on propensity matched multivariable analysis. We must keep in mind, however, the limitations of the NCDB including its retrospective nature and inherent selection bias. The NCDB also lacks important data such as local control, number of brain metastases, Karnofsky performance status, distant brain failure, type and number of cycles of chemotherapy, and any salvage therapy. One could reasonably conclude that patients offered up front SRS likely had higher KPS and more limited brain metastases. However, in this series the likelihood of receiving up front SRS was not increased with younger age, better comorbidity score, or even absence of extracranial metastases. It should be noted that patients receiving chemotherapy had improved survival, likely highlighting a healthier, better performing cohort. Moreover, the fact that use of chemotherapy correlated significantly with OS highlights the aggressive and systemic nature of LCNEC of the lung and vital role of chemotherapy.

Conclusions

In this NCDB analysis, up front treatment of brain metastases from LCNEC of the lung with SRS was associated with improved survival compared to WBRT. Despite the inherent limitations of the NCDB, one can extrapolate from these results that for the appropriately selected patient (younger, absence of extracranial metastases, and ability to receive chemotherapy) up front treatment of limited brain metastases with SRS may be appropriate.

Disclosure statement

None of the authors have any conflict of interest to disclose.

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